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EGFR inhibition triggers an adaptive response against vesicular somatitis virus (VSV) by activating antiviral signaling pathways in human osteosarcoma and glioblastomaEGFR inhibition triggers an adaptive response against vesicular somatitis virus (VSV) by activating antiviral signaling pathways in human osteosarcoma and glioblastoma

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The epidermal growth factor receptor is overexpressed in several cancer types [5]. Several studies revealed the importance of wild-type or mutant EGFR receptors for tumor growth in human cancers. Although, very few studies investigated the role of EGFR in human osteosarcoma [4]. Oncolytic virus (OV) therapy is an emerging anti-cancer approach that uses non-pathogenic viruses to preferentially kill cancer cell [2]. Vesicular stomatitis virus (VSV) is a promising OV because of its well-studied biology, ability to infect a wide range of model and primary cell cultures *in vitro* [3]. In response to viral infection, several signal pathways activate and lead to induction of type I interferons and organization of the antiviral response [1]. Here we demonstrate that EGFR inhibition triggers an antiviral defense pathway in human osteosarcoma. Inhibiting wild-type EGFR triggers type I interferon (IFN)-I upregulation via JAK/ STAT3 or NF-κB signaling pathways [1]. Our results on HOS, DBTRG, U251-MG and primary tumor cell lines show that successful inhibition of EGFR by Gefitinib activates antiviral defense pathway and inhibit VSV infection in osteosarcoma cells. The cytopathic effect of the VSV was compared to the control that was exposed to the same concentration of Gefitinib. Other combinations of Gefitinib, Ruxolitinib (Janus kinase inhibitor) and interferon alfa-2b (recombinant form of the protein Interferon alpha-2) were also used. Replication efficiency and cell viability assays were used to evaluate the intensity of oncolytic effect. The treatment with exogenic interferon protects the cells from VSV and synergizes with the effect of Gefitinib in protection from the oncolytic activity. In contrast, the treatment with Ruxolitinib reverses the protective effect of Gefitinib and increases the cytopathic effect. Our results revealed that inhibition of EGFR in human osteosarcoma leads to antiviral protection against the oncolytic virus VSV. In future, cell lines with mutant versions of EGFR should be analyzed in context of EGFR status and interferon activation levels.

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